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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 09/738,742 | 12/15/2000 | Jason Hill | CUB-4 US | 2149 |
| 34103 | 7590 | 07/09/2004 | EXAMINER | |
| CUBIST PHARMACEUTICALS, INC. 65 HAYDEN AVENUE LEXINGTON, MA 02421 | | | LUKTON, DAVID | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1653 | |
| DATE MAILED: 07/09/2004 | | | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/738,742

Applicant(s)

HILL ET AL.

Examiner

David Lukton

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 27 May 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 2, 5-12, 15-27, 30-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 5-12, 15-27, 30-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/27/04 has been entered.

Pursuant to the directives of the amendment filed 5/27/04, claims 1, 2, 7-11, 16, 23, 27, 30, 31, 34, have been amended. Claims 1, 2, 5-12, 15-27, 30-36 remain pending.

Applicants' arguments filed 5/27/04 have been considered and found persuasive.



The terminal disclaimer filed on 5/27/04 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the patent resulting from application 09/739535 has been reviewed and is accepted. The terminal disclaimer has been recorded.



The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 5-12, 15-27, 30, 33-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Each of claims 1 and 2 is drawn to a compound "having" the indicated formula. The term "having" can be viewed as being "open-ended", with an effect similar to that of the term "comprising". Accordingly, it is asserted that the scope is unduly broad in view of the enabling disclosure.

As stated in *Ex parte Forman* (230 USPQ 546, 1986) and *In re Wands* (8 USPQ2d 1400, Fed. Cir., 1988) the factors to consider in evaluating the need (or absence of need) for "undue experimentation" are the following: quantity of experimentation necessary, amount of direction or guidance presented, presence or absence of working examples, nature of the invention, state of the prior art, relative skill of those in that art, predictability or unpredictability of the art, and breadth of the claims. As it happens, structure/activity relationships of antibacterial compounds are unpredictable. Consider, for example, the following:

- Gavini ("Pyridazine N-oxides. III. Synthesis and in vitro antimicrobial properties of N-oxide derivatives based on tricyclic indeno[2,1- c]pyridazine and benzo[f]cinnoline systems", *Archiv der Pharmazie* **333** (10) 341-6, 2000) discloses the preparation and testing of a series of pyridazine N-oxides. With the exception of compounds 3a, 3b, 4b and 5b, the compounds "demonstrated no activity against bacteria" (page 342, col 2).

- Fudou ("Haliangicin, a novel antifungal metabolite produced by a marine myxobacterium. 1. Fermentation and biological characteristics", *Journal of Antibiotics* **54** (2) 149-52, 2001) discloses the isolation of haliangicin which is produced by a marine bacteria; the compound contains a conjugated tatraene moiety and exhibited no antibacterial activity.
- Juvvadi ("Structure-activity studies of normal and retro pig cecropin-melittin hybrids", *Journal of Peptide Research* **53** (3) 244-51, 1999) discloses the preparation and antibacterial activity of cecropin-melittin hybrid peptides. Also disclosed is that the "retro" analogs (the polarity of the amide bond reversed) lost antibacterial activity.
- Avrahami (*Biochemistry* **40** (42) 12591-603, 2001) studied the effects of amino acid substitutions on the antimicrobial activity of amphipathic antimicrobial peptides. Many of the compounds prepared lost antibacterial activity as a result of a single amino acid substitution. Although after-the-fact rationalizations were provided, the observed structure/ activity relationships could not have been predicted *a priori*.
- Goldman, R. C. (*FEMS Microbiology Letters* **183**(2), 209-214, 2000) discloses (sentence bridging pages 210-211) that removal of an amino acid from a vancomycin eliminates activity.
- Harris, Constance (*Journal of Antibiotics* **38**(1), 51-7, 1985) discloses that replacement of an asparagine residue in vancomycin with isoaspartic acid eliminates activity.

These and other references disclose that there do exist compounds which exhibit no antibacterial activity, and many of these inactive compounds are structurally analogous to compounds that are active. The key point is that the factors which give rise to activity or inactivity are unknown in the art; and certainly the specification has made no attempt to discuss such factors. Accordingly, the skilled microbiologist cannot predict antibacterial

activity merely by viewing a structure

It remains the case that "undue experimentation" would be required to determine which of the claimed compounds can exhibit antibacterial activity.

It is suggested that in claims 1 and 2, the phrase *of the formula* be used rather than "having the formula", and that in claim 8, the phrase "not naturally occurring" be deleted from the definition of substituent variable R⁸.



Claims 23 and 24 are objected to. The Trademarks should be capitalized (e.g., ZIRACIN, SYNERCID, EPIROPRIM).



Claims 1, 2, 5-12, 15-27, 30-36 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In each of claims 1 and 2, a formula is provided which contains the variable (X)_n. However, "n" can assume only one value (unity). Accordingly, making reference to "(X)_n" and then defining "n" as 1 is superfluous. It is suggested that variable "X" be used rather than (X)_n.
- Claim 19 makes reference to "antibiotic-resistant bacteria". Is this intended to include resistance to the claimed compounds? It is suggested that the limitations of claim 20 be introduced into claim 19.
- Claim 21 makes reference to a "compound of formula (I)". Which version of

formula I is being referred to...?

- The clarity of claim 22 would be improved by making reference to *a second antimicrobial agent*. Following is language that could be used for claims 22 and 23:

22R. The method comprising the step of co-administering a second antimicrobial agent... wherein said second antimicrobial agent is not included within the scope of formula (I).

23R. The method according to claim 22, wherein said second antimicrobial agent is selected from the group consisting of...

- In claim 23, the term "synthetic antibacterials" is used, but this overlaps with the other terms recited, thus generating a redundancy. It is suggested that the phrase at issue be deleted.



Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber, can be reached at 571-272-0925. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

D. Lukton

DAVID LUKTON
PATENT EXAMINER
GROUP 1803